

REMARKS

Claims 1-3, 5, 6, 11-13, 23-26, and 49-81 constitute the pending claims in the present application, prior to Amendment. Claims 1, 2, 6, 23, 25, 26, 49, 50, 52, 53, 63, and 64 have been amended to improve the clarity of the claims and to delete explicit reference to non-elected subject matter. Claims 66-81 have been amended to more particularly point out the claimed subject matter.

Applicants' amendments are fully supported by the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appeared in the Office Action.

Continued Examination Under 37 CFR 1.114

Applicants note that the finality of the previous Office Action has been withdrawn in view of the Request for Continued Examination and reply filed November 5, 2007.

Election / Restriction

Applicants note that the Examiner has made the Restriction Requirement final, and that claims 1-3, 5, 6, 11-13, 23-26, and 49-81 will be examined on their merits in so far as they are drawn to SEQ ID NO: 13.

Applicants reiterate for the record the timely traversal of the Restriction Requirement. Further, Applicants reiterate that claims 66-81 are linking claims for the inventions of Groups I-IV. In accordance with MPEP 809, upon allowance of a generic claim, all claims properly dependent thereon must be considered.

Claim Objections

Claims 1, 2, 6, 23, 25, 26, 49, 50, 53, 63, and 64 are objected to for reciting non-elected subject matter. Applicants maintain that consideration by the Examiner of claims reciting more than a single Sonic hedgehog sequence does not constitute an undue burden. Nevertheless, to expedite prosecution, Applicants have amended claims 1, 2, 6, 23, 25, 26, 49, 50, 53, 63, and 64 to reference only the elected sequence. Applicants' amendment is not for reasons related to the patentability of the claims and does not alter the scope or interpretation of the Sonic hedgehog

polypeptides (described with reference to SEQ ID NO: 13 or using means-plus-function language) for use in the claimed methods. Reconsideration and withdrawal of this objection is requested.

Priority

The Examiner's analysis of the effective filing date of the instant claims is not relevant to the arguments advanced in the instant response, and thus is not addressed herewith. Applicants traverse and reserve the right to refute or otherwise address the Examiner's priority analysis in this or in futures applications, or in the course of Appeal or litigation.

35 U.S.C. 112, first paragraph, written description

Claims 1-3, 11-13, 23-24, and 49-81 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The first basis of the rejection is articulated in the paragraph spanning pages 5 and 6 of the instant Office Action and is based on recitation of "an amino acid sequence designated in (instantly-elected) SEQ ID NO: 13, or an N-terminal fragment thereof having a molecular weight of approximately 19 kDa". (emphasis added). The Examiner has interpreted this phrase as encompassing amino acid sequences of as few as two residues. Applicants respectfully disagree.

Claims must be given their broadest *reasonable* interpretation, and Applicants contend that one of skill in the art would not interpret the claims in the manner interpreted by the Examiner. Nevertheless, to expedite prosecution, Applicants have amended the claims to refer to "the amino acid sequence designated in SEQ ID NO: 13, or an N-terminal fragment thereof having a molecular weight of approximately 19 kDa." Applicants' amendment is believed to clarify the reasonable interpretation of the claim. Applicants' amendment is made solely for clarity, and does not alter the scope of the claims, when the claims are given their broadest reasonable interpretation. Applicants' amendment is not in acquiescence to the rejection.

The rejection is additionally based on the alleged correlation between the structure and function of the polypeptides for use in the claimed method. Once again, Applicants respectfully disagree. However, the above clarifying amendment is believed to largely address the Examiner's concern. Additionally, Applicants have amended claims 1, 2, and 23 to clarify that

the recited functional description (binds to a naturally occurring hedgehog receptor and promotes hedgehog signaling) refers to the recited amino acid sequences, and not just to the polypeptide as a whole. In other words, the Sonic hedgehog polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 13, or an N-terminal fragment thereof of approximately 19 kDa, can bind to a naturally occurring hedgehog receptor via the recited amino acid sequence (via the amino acid sequence of SEQ ID NO: 13, or an N-terminal fragment thereof of approximately 19 kDa). Applicants' amendment is believed to clarify the relationship between the structure and function of polypeptides comprising the recited amino acid sequences.

Applicants take this opportunity to correct the record with respect to statements made in the paragraph spanning pages 6 and 7 of the Office Action. Specifically, the Examiner states that the auto-proteolytic fragment described in the specification is "about Cys-198 through Ala-475 of the human Shh protein." The Examiner has correctly identified the C-terminal fragment, as described in the specification. However, the Examiner has failed to refer to the N-terminal fragment that is also explicitly described in the specification and recited in the claims. See, for example, paragraphs [0096] and [0097] of the published specification. Applicants' specification described the cleavage event that processes the 475 amino acid version of the hedgehog protein into an N-terminal domain having a molecular weight of approximately 19 kDa and a somewhat larger C-terminal domain having a molecular weight of approximately 27 kDa. Accordingly, the Examiner's arguments advanced on pages 6-8 regarding possession of N-terminal fragments of SEQ ID NO: 13 having a molecular weight of approximately 19 kDa are misplaced and based on an incomplete recognition of Applicants' disclosure.

The second basis of the rejection concerns claims 49 and 52. Applicants reiterate the arguments detailed above, and have made corresponding amendments to claims 49 and 52. As such, the claims are believed to be fully compliant with the written description requirement.

The third basis of the rejection concerns claims 66-81. Applicants note that claims 66-81 are means-plus-function claims in compliance with 35 U.S.C. § 112, sixth paragraph. As is clear from the very language of the statute, claims interpreted under 35 U.S.C. § 112, sixth paragraph, are construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. Thus, the claims are so intimately tied to the disclosure of the specification – for the specification lays the foundation for the scope of the claim in an intimate and inextricable manner – that the claims by definition must be adequately described. Further,

the MPEP even provides guidance regarding examination of equivalents that fall within the scope of means-plus-function claims. MPEP 2182: “The specification need not describe the equivalents of the structures, material, or acts corresponding to the means- (or step-) plus-function claims. See *In re Noll*, 545 F.2d 141, 149-50, 191 USPQ 721, 727 (CCPA 1976) (‘The meaning of “equivalents” is well understood in patent law, … and an applicant need not describe in the specification the full range of equivalents of his invention.’ (citation omitted).’)

Applicants submit that there is no basis in law to reject means-plus-functions claims for allegedly failing to comply with the written description requirement. Nevertheless, to expedite prosecution and to clarify the claims, Applicants have amended claims 66-81 to specify that the “means” recited in the claims is a means for binding a naturally occurring hedgehog receptor and thereby promoting hedgehog signaling.

The Office Action cites several cases, such as *Fiers. v. Revel, Amgen Inc. v. Chugai*, and *Fiddes v. Baird*, for the proposition that the compounds recited in the claims are not adequately described. These cases, however, are inapposite, because the claims considered in those applications were not method claims, as are the pending claims, but were directed to protein and nucleic acid sequences. “Possession”, as contemplated by the written description requirement, refers not to *physical* possession but to *conceptual* possession. The standard for measuring sufficiency of the written description, as articulated in *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989), was quoted in *Vas-Cath v. Mahurkar*, already cited by the Examiner:

A fairly uniform standard for determining compliance with the ‘written description’ requirement has been maintained throughout: ‘Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.’

While *Amgen v. Chugai* stands for the proposition that a nucleic acid is not conceived until the sequence is known, case law does not support the extension of this holding to method claims such as those presented by Applicants. Applicants are not aware of, nor does the Office Action cite, *any* cases holding that a *method* is not conceived until reduction to practice occurs, as the Office Action asserts.

The Office Action further asserts that “one must still be able to envision the class of compounds based on the written description of the specification.” This statement is not supported by case law, either explicitly, or by any cases of which Applicants are aware. The Office Action

does not allege that the limitations and features of the claims are not literally supported by the specification. Methods are not subject to the doctrine of simultaneous conception and reduction to practice that applies when nucleic acids and proteins are claimed as compositions of matter. Instead, methods such as those claimed can be conceived independently and are constructively reduced to practice, at the very least, by the filing of a patent application. Applicants submit that the specification as filed fully supports Applicants' conception of the subject matter of the pending claims at the time of filing of the present application as required by 35 U.S.C. § 112, first paragraph.

In view of the foregoing arguments and amendments, Applicants submit that the pending claims are fully compliant with the written description requirement. Reconsideration and withdrawal of this rejection are requested.

35 U.S.C. 112, first paragraph, enablement

Claims 1-3, 5, 6, 11-13, 23-26, and 49-81 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The basis of the rejection appears to be two-fold. First, the rejection appears to be based on whether the claims are enabled for the use of the full scope of Sonic hedgehog polypeptides allegedly encompassed by the claims. Second, the rejection appears to be based on whether the claims are enabled throughout the full scope of the claimed methods of promoting proliferation, differentiation, and/or survival of the recited cell types.

As detailed above, Applicants have amended the claims to clarify the scope of the hedgehog polypeptides for use in the claimed methods. Although it is difficult for Applicants to share the Examiner's interpretation of the claims, prior to Amendment, as encompassing polypeptides having as few as two amino acids, Applicants' amendments to the claims clarify that such an idiosyncratic interpretation is not the intended meaning of the claims. Applicants contend that the first basis for the rejection is addressed and obviated by Applicants' amendments to the claims.

In outlining the second basis of the rejection, the Examiner reviews the Wands factors and alleges that the claimed invention is not enabled based on consideration of the Wands factors. As an initial point, Applicants disagree with the evaluation of the Wands factors, as well

as the conclusion, unsupported by evidence, that the claims fail to comply with the enablement requirement. Applicants do not acquiesce to any of the statements or conclusions advanced in the Office action. In addition to the arguments detailed in this response, Applicants reserve the right to produce additional evidence and make additional detailed arguments to address the Examiner's analysis.

Applicants respectfully submit that the Examiner's analysis of the Wands factors provides no indication of whether and how the Examiner has weighed the extensive post-filing evidence provided to support the enablement of the claimed subject matter. Rather, the review of the Wands factors provided on pages 11-15 of the Office Action offers nothing more than conclusory statements unsupported by objective evidence and without an assessment of how the evidence and arguments provided by Applicants' were balanced or considered.

Over the course of the last several responses, Applicants have advanced numerous scientific and legal arguments, and have cited objective post-filing evidence to support Applicants' position that the claims are enabled throughout their scope. Applicants' post-filing evidence includes affidavits. Applicants have also put forth arguments specifically undermining the position allegedly supported by the evidence cited by the Examiner (e.g., the Miao and Traiffort references relied upon as part of the enablement rejection set forth in the Office Action mailed August 24, 2007). The instant rejection reviews the Wands factors without any indication of whether and how the arguments and evidence of record have been considered. Applicants respectfully submit that this is improper and fails to satisfy the Office's burden for properly maintaining this rejection.

In accordance with MPEP 2164.04, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Further, even in cases where the Examiner has met their initial burden to reasonably question enablement, the ultimate determination of enablement must be based on the evidence as a whole. MPEP 2164.05. Applicants respectfully submit that the instant rejection provides no indication of whether and how the evidence of record was weighed and evaluated. In fact, the arguments advanced in Applicants' response filed October 31, 2007 were not addressed in any way in the instant Office Action. Rather, the analysis of the Wands factors provided in the instant Office Action offered nothing more than alleged conclusions, unsupported by objective evidence. Applicants fail to

appreciate how unsupported conclusions can outweigh the arguments and objective evidence advanced by Applicants throughout prosecution.

Applicants respectfully submit that the Examiner has not satisfied the burden necessary to maintain this rejection in the face of the teachings of the specification and objective evidence provided by Applicants. As such, reconsideration and withdrawal of this rejection is requested. If the Examiner maintains this rejection, Applicants respectfully request clarification of the Office's position, including an explanation for why Applicants' evidence and arguments are deemed unpersuasive, so that Applicants can specifically address the Examiner's concerns. Applicants submit that any such clarification such occur via a non-final Office action.

Related Applications

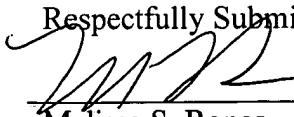
Applicants take this opportunity to bring the following co-pending, commonly assigned applications to the Examiner's attention: application serial numbers 11/197,721; 11/634,358; and 11/894,601. These co-pending applications have already been made of record and their corresponding publications cited in an Information Disclosure Statement. The Examiner is invited to consider previous, current, or future prosecution in the co-pending applications.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. HMSU-P17-006.**

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Respectfully Submitted,



Melissa S. Rones
Reg. No. 54,408
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050